Abstract
Cryptands with sucrose scaffold, an unknown class of such derivatives, were prepared from the readily available 2,3,3’,4,4’-penta-O-benzylsucrose and 1’,2,3,3’,4,4’-hexa-O-benzylsucrose.

Introduction
The design and synthesis of macrocyclic receptors is one of the main challenges of supramolecular chemistry [1,2]. These artificial systems exhibit interesting properties and find many applications in, e.g., selective complexation of ionic and neutral species, medicinal chemistry (as drug carriers), and in the synthesis (as phase transfer catalysts). The complexing properties depend on several crucial parameters such as cavity size, type of heteroatoms involved in the ring, functional groups etc.

Carbohydrates are especially useful platforms for macrocycles being able to recognize enantiomers. Special attention is directed to native and modified cyclodextrins, cyclic oligosaccharides, which have found wide application in many aspects of chemistry and industry [3,4]. There are also reports on the preparation of ‘distorted’ cyclodextrins in which diverse fragments are incorporated into the original oligosaccharide ring(s) [5]. Another class of sugar receptors is represented by macrocyclic derivatives with the carbohydrate unit being a part of a crown or aza-crown structure. Up to date, only monosaccharides have been intensively used as chiral building blocks in the synthesis of such macrocycles. Less attention, however, has been paid to macrocycles with disaccharides (or oligosaccharides) being a part of the ring [6-8].

We have proposed to use sucrose (1) as a convenient chiral platform for such macrocycles [9,10]. Several of them, such as 5 (Figure 1), are able to differentiate enantiomers of α-phenylethylammonium salt [11,12]. Sucrose dimers containing two urea or thiourea units (6 or 7) are able to complex anions [13,14]. More complex derivatives with sucrose scaffold (e.g., 4) can be also prepared successfully [15,16].
All macrocyclic derivatives, shown in Figure 1, were prepared from hexa-O-benzylsucrose 3 by a connection of the terminal positions of glucose (C6) and fructose (C6') units.

Results and Discussion
Diol 3 may be also used as a starting material for the preparation of cryptands containing a sucrose platform, a completely new class of such derivatives. This goal can be achieved by introduction of an additional macrocyclic unit connecting both terminal positions as shown in Figure 2. The direct connection of both CH₂-OH groups (route a in Figure 2) is, however, problematic, because of steric hindrance.

The approach shown on route b (Figure 2), in which the terminal positions are elongated to avoid these difficulties, seems to be more feasible.

Diol 3 was, thus, extended at both terminal positions by five atoms by reaction with bis(2-chloroethyl) ether; this process provided an intermediate 9 in good yield. Replacement of both
terminal chlorine atoms by iodine afforded compound 10, which was reacted with commercially available diaza-crown ether 8 to afford the first sucrose cryptand 11 in excellent yield (33%, Scheme 1).

The structure of this first sucrose cryptand, suggested by HRMS analysis \([m/z = 1285.6803\) which corresponds to \((C_{74}H_{97}N_2O_{17} + H^+))\], was confirmed by the NMR data. In the \(^{13}\)C NMR spectrum of the final compound, six characteristic signals at \(\delta \approx 50–60\) ppm were observed. They can be assigned to the methylene groups connected to the nitrogen atoms (-CH$_2$-N units), and thus this observation confirms the presence of the crown-unit 8 in the structure.

Although the first approach to sucrose cryptands was very successful, the strategy based on sucrose diol 3 has several limitations. First of all, the cavity in cryptand 11 is large and – since it is accessible from both sides of the molecule – it may decrease the complexing properties especially of chiral guests.

To differentiate substantially both sides of the molecule, another type of cryptand is needed, in which all three terminal positions (C1', C6, C6') are connected. This goal can be realized starting from sucrose triol 2 as shown in Figure 3.

The first approach consists of a connection of the C1’-position of an intermediate aza-crown ether 12 with the secondary nitrogen atom present in a linker (route a in Figure 3). Another one (route b in Figure 3) involves a direct coupling of all three positions: C1’, C6, C6’.

Recently we have proposed a convenient method for the conversion of triol 2 into a number of sucrose macrocycles having various substituents at the C1’-position [17,18]. Modification of these synthetic routes should allow, eventually, the preparation of derivative 12 in which the C1’ and the ring nitrogen atom might be connected to form cryptand 13 (route a; Figure 3). However, we have found that the preparation of a suitable aza-crown intermediate 12 with the secondary amine function in the linker and the properly modified C1’-position caused substantial problems. We decided, therefore, to prepare sucrose cryptands according to route b, i.e., to connect all three terminal positions at the same time.

The first attempt was, however, unsuccessful. Activation of all terminal hydroxy groups as mesylates and subsequent reaction of such intermediate 14 with tripodal amine 15 [19] did not provide the desired cryptand 16 (Scheme 2); the starting material remained unchanged.

This fact may result either from the steric hindrance or the very low reactivity of the hydroxymethylene group [20,21]. We decided, therefore, to elongate the sucrose skeleton by two carbon atoms at the C-1’ position as well as at other terminal positions. Thus, all three hydroxy groups were protected as allyl ethers which were subsequently converted into -CH$_2$-CH$_2$OH units (Scheme 3). Activation of the free OH groups in 18 as

**Scheme 1:** a) 50% NaOH, Bu$_4$NHSO$_4$, 74%; b) Nal, acetone, 95%; c) Na$_2$CO$_3$, ACN, 80 °C, 24 h, 33%.
mesylates 19 and subsequent reaction with tripodal amine 15 afforded cryptand 20 (Scheme 3). Its presence was confirmed by HRMS \([m/z = 1287.7020]\) which corresponds to \([C_{86}H_{94}N_{4}O_{11} + H^+]\) but the NMR spectrum of 20 was difficult for interpretation because it showed very dynamic changes. Many signals in the \(^1H\) NMR as well as \(^{13}C\) NMR spectra overlapped which made the full analysis difficult. However, the presence of three characteristic signals at \(\delta \approx 60\) ppm in the \(^{13}C\) NMR spectrum, which can be assigned to the \(-NCH_2Ph\) fragments, fully confirmed the presence of a tripodal amine 15 fragment in the structure of the cryptand.

The method presented in Scheme 3 can be also applied to prepare cryptands with larger cavities. This required an elongation of all three terminal positions (at C1', C6, C6') by a longer linker. Thus, reaction of triol 2 with bis(chloroethyl) ether provided derivative 21 in good yield. Replacement of the chlorine atoms for iodine gave 22 which was subjected to the reaction with tripodal amine 15.

The cyclization reaction provided cryptand 23 in very high yield: 45.5% (Scheme 4). The structure of the cryptand was confirmed by HRMS \([m/z = 1419.7803]\) which corresponds to...
(C_{86}H_{107}Na_{14} + Na^+)]. Further confirmation came from the $^{13}$C NMR data. In the spectrum recorded in acetone-$d_6$, three signals at $\delta \approx 60$ ppm were seen. These signals were assigned (by HSQC experiments) to the benzyl groups connected to nitrogen atoms (-NH$_2$Ph), thus finally confirming the presence of a tripodal unit in the structure of the cryptand.

**Conclusion**

We proposed convenient routes to a completely new class of macrocyclic derivatives: cryptands with sucrose scaffold. Such cryptands can be prepared either from a ‘sucrose diol’ (hexa-O-benzylsucrose) by introduction of an additional macrocyclic unit connecting the terminal positions, or ‘sucrose triol’ (penta-O-benzyl-sucrose). The latter approach is probably more convenient since it allows preparing cryptands of various size of cavity just by simple elongation of all three terminal positions with linkers of different size. In our model studies we have elongated these positions with the same linker. However, since all three terminal positions can be differentiated (as we have proven during our earlier studies see ref. [10]), it is possible to introduce different linkers at the C1’, C6, and C6’ fragments. Thus, our first syntheses of cryptands from ‘sucrose triol’ may open a possibility to prepare such structures with different size depending on the need.

**Experimental**

**General**

NMR spectra were recorded in CDCl$_3$ (internal Me$_4$Si) with a Varian AM-600 (600 MHz $^1$H, 150 MHz $^{13}$C) spectrometer at rt unless otherwise stated. Chemical shifts ($\delta$) are reported in ppm relative to Me$_4$Si ($\delta$ 0.00) for $^1$H and residual chloroform ($\delta$ 77.00) for $^{13}$C. All significant resonances (carbox skeleton) were assigned by COSY ($^1$H–$^1$H), HSQC ($^{13}$C–$^1$H), and HMBC ($^1$H–$^{13}$C) correlations. Reagents were purchased from Sigma-Aldrich, Alfa Aesar or ABCR, and used without purification. Hexanes (65–80 °C fraction from petroleum) and EtOAc were purified by distillation. All other commercially available solvents were used without purification. Thin-layer chromatography was carried out on silica gel 60 F$_{254}$ (Merck). Column chromatography was performed on silica gel 60 (70–230 mesh, Merck). Flash chromatography was performed on Büchi glass columns packed with silica gel 60 (230–400 mesh, Merck), using a Knauer Smartline system with a Büchi fraction collector. The organic solutions were dried over MgSO$_4$ or Na$_2$SO$_4$. Optical rotations were measured with a Jasco P 1020 polarimeter (sodium light) in chloroform at room temperature.

$^{1}$,2,3,3',4,4'-Hexa-O-benzyl-6,6'-bis[2-(2-chloroethoxy)ethyl]sucrose (9): A solution of compound 3 (100 mg, 0.11 mmol) and tetrabutylammonium hydrogen sulfate (38.5 g, 0.11 mmol) in bis(2-chloroethyl) ether (284 µL, 2.42 mmol) was vigorously stirred with 50% NaOH solution (423 µL) at room temperature for 3 h. Then CH$_2$Cl$_2$ (1.5 mL) and water (1.5 mL) were added, the organic layer was separated and the aqueous one extracted with CH$_2$Cl$_2$ (2 × 5 mL). The combined organic solutions were washed with water (2 × 5 mL), dried, and concentrated under high vacuum to remove excess of bis(2-chloroethyl) ether. The crude material was purified by column chromatography (hexane/ethyl acetate 80:20) to afford the title product 9 (92 mg, 0.08 mmol, 74%) as an oil. $\alpha$ = +29.9; $^1$H NMR $\delta$ 5.66 (d, $J_{1,2}$ = 3.6 Hz, 1H, H-1), 4.90 (d, $J$ = 10.9 Hz, 1H, OCH$_2$Ph), 4.86 (d, $J$ = 11.0 Hz, 1H, OCH$_2$Ph), 4.76 (d, $J$ = 10.9 Hz, 1H, OCH$_2$Ph), 4.67 (d, $J$ = 11.4 Hz, 1H, OCH$_2$Ph), 4.64 (dd, 2H, OCH$_2$Ph), 4.58–4.54 (m, 4H, OCH$_2$Ph), 4.52 (d, $J$ = 11.4 Hz, 1H, OCH$_2$Ph), 4.44–4.40 (m, OCH$_2$Ph, 2H, H-3’), 4.10 (m, 2H, H-4’, H-5’). 4.04 (ddd, $J$ = 10.2, 3.3, 1.9 Hz, 1H, H-5), 3.94 (t, $J$ = 9.3 Hz, 1H, H-3), 3.75 (d, $J$ = 11.0 Hz, 1H, H-1’a), 3.72–3.45 (m, 21H, OCH$_2$Ph, H-4, H-2, 2 × CH$_2$Cl), 3.42 (dd, $J$ = 10.8, 1.8 Hz, 1H, H-6a) ppm; $^{13}$C NMR $\delta$ 138.9, 138.8, 138.4, 138.3, 138.3, 137.9 (C$_{quat}$, 6 × OCH$_2$Ph), 104.7 (C-2’), 90.2 (C-1’), 83.9 (C-3’), 82.6 (C-4’), 81.9 (C-3), 79.8 (C-2), 79.8 (C-5’), 77.5 (C-4), 75.5, 74.8, 73.4, 72.9, 72.3 (5 × OCH$_2$Ph), 72.7 (C-6’), 72.4, 71.4, 71.3, 71.0, 70.8, 70.5, 70.5 (C-7, C-8, C-9, C-7’, C-8’, C-9’, C1’), 70.6 (C-5’), 69.7 (C-6), 42.8, 42.7 (2 × CH$_2$Cl) ppm; HRMS (ESI) [M + Na]$^+$ calcd for C$_{62}$H$_{72}$O$_{13}$Cl$_2$Na, 1117.4248; found, 1117.4211; anal. calcd for C$_{62}$H$_{72}$O$_{13}$Cl$_2$ (1096.15): C, 67.94; H, 6.62; Cl, 6.43; found: C, 67.94; H, 6.85; Cl, 6.43.
(C-6), 3.1, 2.9 (2 × CH$_2$) ppm; HRMS (ESI) [M + Na]$^+$ calc. for C$_{26}$H$_2_2$O$_{11}$Na$_2$, 310.2960; found, 310.2955; anal. calc. for C$_{35}$H$_{2_2}$O$_{13}$I$_2$ (1279.05): C, 58.22; H, 5.67; I, 19.84; found: C, 58.12; H, 5.67; I, 19.79.

**Cryptand 11:** To a solution of 10 (258 mg, 0.20 mmol) in acetonitrile (7 mL), powdered potassium carbonate (342 mg, 3.227 mmol, 16 equiv) was added, followed byaza-crown 8 (53 mg, 0.20 mmol, 1 equiv), and the mixture was stirred and boiled under reflux for 24 h (TLC monitoring: dichloromethane/methanol 10:1). The reaction mixture was then cooled to room temperature, diluted with toluene (5 mL), and acetonitrile was removed in vacuum. The remaining toluene solution was passed through a short pad of Celite, concentrated, and the residue was purified by flash chromatography (dichloromethane/methanol 100:0→96:4) to afford derivative 11 (87 mg, 0.07 mmol, 33%) as an oil; $^1$H NMR (acetone-d$_6$) δ 5.84 (d, $J$ = 3.7 Hz, 1H, H-1''), 4.95 (d, $J$ = 11.2 Hz, 1H, OCH$_2$Ph), 4.85 (d, $J$ = 11.3 Hz, 1H, OCH$_2$Ph), 4.82–4.77 (m, 4H, OCH$_2$Ph), 4.72 (d, $J$ = 12.1 Hz, 1H, OCH$_2$Ph), 4.64 (d, $J$ = 10.8 Hz, 3H, OCH$_2$Ph), 4.61 (d, $J$ = 11.3 Hz, 1H, OCH$_2$Ph), 4.58 (d, $J$ = 12.0 Hz, 1H, OCH$_2$Ph), 4.52 (d, $J$ = 7.9 Hz, 1H, H-3''), 4.40 (t, $J$ = 8.1 Hz, 1H, H-4''), 4.06 (dt, $J$ = 10.4, 2.6 Hz, 1H, H-5'), 3.97 (dd, $J$ = 8.0, 5.0, 2.7 Hz, 1H, H-5''), 3.92 (t, $J$ = 9.3 Hz, 1H, H-3), 3.84 (dd, $J$ = 11.2, 2.8 Hz, 1H, H-6'a), 3.80 (dd, $J$ = 11.2, 5.1 Hz, 1H, H-6'b), 3.75 (d, $J$ = 10.8 Hz, 1H, H-1'a), 3.62 (d, $J$ = 10.74 Hz, H-1''b), 3.51 (m, 1H, H-4), 3.48 (dd, $J$ = 9.6, 3.7 Hz, 1H, H-2''), 3.43 (m, 2H, H-6'a, H6'b) ppm; $^{13}$C NMR (acetone-d$_6$) δ 104.1 (C-2''), 117.2 (C-1'), 125.7, 125.5, 116.1 (C-17), 137.9, 137.7, 137.4, 137.3 (C$_{quat}$, 5 × OCH$_2$Ph), 133.7 (C-9), 133.7 (C-9'), 133.5 (C-7'), 116.2 (C-8), 116.1 (C-7'), 115.9 (C-8'), 103.6 (C-2'), 89.1 (C-1), 82.9 (C-3'), 81.7 (C-4'), 80.9 (C-3), 78.8 (C-2), 78.6 (C-5'), 76.6 (C-4), 74.5, 73.8, 72.0, 71.5 (5 × OCH$_2$Ph), 71.4 (C-8), 71.4 (C-7), 71.2 (C-7'), 70.5 (C-6), 69.5 (C-5), 67.4 (C-6) ppm; anal. calc. for C$_{35}$H$_{2_3}$O$_{11}$ 1210.5860; found, 1210.5839.

**1',6',6'-Tri-O-allyl-2,3,3',4,4'-penta-O-benzylisourocrose (17):** To a solution of triol 2 (88 mg; 0.11 mmol) in toluene (3 mL), allyl bromide (56 µL, 0.66 mmole, 6 equiv) was added followed by 50%aq NaOH (3 mL), and the heterogeneous mixture was vigorously stirred at 50 °C for 18 h (TLC monitoring hexane/ethyl acetate 4:1). The mixture was diluted with toluene (10 mL), the organic phase was separated, dried, and the product was purified by chromatography (hexane/ethyl acetate 100:0→70:30) to afford 17 (96 mg, 0.19 mmol, 94%) as an oil. [α]$_D$ = +37.2; $^{1}$H NMR δ 5.59 (d, $J_{12,1'}$ = 3.5 Hz, 1H, H-1), 4.36 (d, $J_{12,1'}$ = 7.3 Hz, 1H, H-3), 4.29–4.22 (m, 6H, H-6'a, H-6'b, H β-β, H-7'a, H-7'b), 4.05 (t, $J_{12,1'}$ = 7.3 Hz, 1H, H-4''), 3.95 (t, $J_{12,1'}$ = 9.3 Hz, 1H, H-3), 3.73–3.63 (m, 7H, H-6'a, H-6'b, H-7'a, H-7'b), 3.59–3.54 (m, 4H, H-4, H-6'a, H-7'a, H-7'b), 3.50 (dd, 1H, H-2'), 3.47 (d, $J_{12,1'}$ = 11.2 Hz, 1H, H-1'), 3.41 (dd, $J_{6'a,6'b}$ = 10.8, J$_{6'b,6'a}$ = 1.5 Hz, 1H, H-6'b), 2.95 (s, 3H, CH$_3$SO$_2$), 2.93, 2.92 (s, 3H, CH$_3$SO$_2$); $^{13}$C NMR δ 138.6,
138.4, 138.2, 137.9, 137.9 (C_{quat}, 5 \times OCH_2Ph), 104.3 (C-2'), 90.1 (C-1), 83.4 (C-3'), 81.9 (C-4'), 81.8 (C-3), 79.8 (C-2), 79.6 (C-5'), 77.4 (C-4), 75.5, 74.9, 73.0, 72.8, 72.4 (5 \times OCH_2Ph), 72.5 (C-6'), 72.2 (C-1'), 70.6 (C-5), 69.9 (C-6), 69.3 (C-α), 69.2 (C-7), 69.0 (C-7'), 68.9 (C-8'), 68.7 (C-8), 68.6 (C-β), 37.5, 37.5, 37.4 (3 \times CH_3SO_3) ppm; HRMS (ESI) [M + Na]^+ calculated for C_{56}H_{70}O_{14}Cl_3Na, 1133.3964; found, 1133.3960; analyzed calculated for C_{56}H_{70}O_{14}Cl_3Na (1121.57): C, 63.69; H, 6.57; Cl, 9.56; found: C, 63.69; H, 6.61; Cl, 9.56.

Synthesis of cryptand 20: To a solution of 19 (141 mg; 0.12 mmol) in acetonitrile (10 mL), tripodal amine 15 (55 mg, 0.13 mmol, 1.1 equiv) was added, and the mixture was stirred at 80 °C for 24 h (TLC monitoring dichloromethane/methanol 10:1). After cooling to rt, the mixture was concentrated and the resulting cryptand was purified by chromatography (dichloromethane/methanol 100:0→96:4), to give derivative 21 (103 mg; 80% yield) as an amorphous solid. Methane/methanol 100:0 to 96:4), to afford derivative 21 (103 mg; 80% yield) as an amorphous solid. To a solution of triol (1158.34): C, 58.02; H, 6.09; S, 8.30; found: C, 58.0; H, 6.17; S, 8.30.

Synthesis of cryptand 23: To a solution of 22 (118 mg, 0.09 mmol) in acetonitrile (15 mL), powdered potassium carbonate (270 mg, 2.55 mmol, 30 equiv) was added, followed by amine 15 (40 mg, 0.09 mmol, 1.1 equiv), and the mixture was stirred and boiled under reflux for 24 h (TLC monitoring: dichloromethane/methanol 10:1). The mixture was cooled to room temperature, diluted with tolune (15 mL), and acetonitrile was removed in vacuum. The toluene solution was then filtered through a short pad of Celite, the filtrate was concentrated, and the residue was purified by flash chromatography (dichloromethane/methanol 100:0→93:7) to afford derivative 23 (55 mg, 0.04 mmol, 45.5%) as an oil. HR NMR (acetone-d6) δ 5.76 (d, J_{1,2} = 5.55 Hz, 1H, H-1), 4.99 (d, J = 11.01 Hz, 1H, OCH_2Ph), 4.88 (d, J = 11.38, 1H, OCH_2Ph), 4.91 (d,
\[ J = 10.98 \text{ Hz}, \ 1H, \ \text{OCH}_2\text{Ph}, \ 4.81 \ (d, \ J = 11.05 \text{ Hz}, \ 1H, \ \text{OCH}_2\text{Ph}), \ 4.71–4.59 \ (m, \ 5H, \ \text{OCH}_2\text{Ph}), \ 4.44 \ (m, \ 2H, \ H-3'), \ \text{OCH}_2\text{Ph}), \ 4.05–4.00 \ (m, \ 3H, \ H-4', \ H-5', \ H-5), \ 3.96 \ (t, \ J = 9.24 \text{ Hz}, \ 1H, \ H-3), \ 3.87 \ (d, \ J = 11.04 \text{ Hz}, \ 1H, -\text{OCH}_2'), \ 3.82 \ (dd, -\text{OCH}_2'), \ 3.70–3.36 \ (m, \ 32H, -\text{OCH}_2', -\text{NCH}_2-, \ H-2, \ H-4), \ 3.21–2.54 \ (m, \ 16H, -\text{OC}_2\text{H}_5\text{Ph}), \ 3.25 \ (m, \ 8 \times \text{CH}_2\text{Ph}), \ 3.13 (s, 3 \times \text{NCH}_3\text{H}), \ 3.06 (s, 2 \times \text{CH}_3), \ 3.02 (s, 2 \times \text{C}'), \ 2.99–2.93 (m, 5 \times \text{NCH}_2\text{Ph}), \ 2.60 (C-5), \ 59.3, \ 59.3, \ 57.3 (3 \times \text{NCH}_2\text{Ph}), \ 51.9, \ 51.2, \ 49.5, \ 49.2, \ 49.2, \ 48.1, \ 47.8 (9 \times \text{NCH}_2-) \text{ ppm}; \ \text{HRMS (ESI)} \ [\text{M + Na}]^+ \text{ calc'd for } \text{C}_{86}\text{H}_{107}\text{N}_4\text{O}_{14}\text{Na}, \ 1419.7784, \text{ found, 1419.7803.}

Supporting Information

Supporting Information File 1
Copies of NMR spectra.

https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-15-20-S1.pdf

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References


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